Final Report

3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery

PREPARED FOR:
Roberts Pharmaceutical Corporation

COVANCE STUDY NUMBER:
6988-101

VOLUME:
1 of 1

COVANCE
THE DEVELOPMENT SERVICES COMPANY

Sponsor:

Roberts Pharmaceutical Corporation
4 Industrial Way West
Eatontown, New Jersey 07724-2274

FINAL REPORT

Study Title:

3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery

Author:

Michael D. DuVall, DVM, PhD

Study Completion Date:

Performing Laboratory:

Covance Laboratories Inc.
9200 Leesburg Pike
Vienna, Virginia 22182-1699

Laboratory Study Identification:

Covance 6988-101

COMPLIANCE STATEMENT

3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery

This study, as performed by Covance Laboratories Inc., was conducted in compliance with the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations Part 58, issued December 22, 1978 (effective June 20, 1979), and with any applicable amendments.

Michael D. DuVall, DVM, PhD
Study Director

Date

QUALITY ASSURANCE STATEMENT

3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery

Quality Assurance inspections and reviews of this study were conducted according to the standard operating procedures of the Quality Assurance Unit and according to the Good Laboratory Practice regulations of the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations, Part 58, issued December 22, 1978 (effective June 20, 1979) and with any applicable amendments. These inspections and reviews were performed and findings were reported to the Study Director and management as follows:

Dates of Inspection/Review	Dates Findings Reported	Inspector/Reviewer
Protocol Review:		
		N. Strickland
Inspection and/or Data Review:		
(Dosing)		N. Strickland
(Data)		C. Allman
(Necropsy)		N. Strickland
(Data)		N. Strickland
(Data)		N. Strickland
Report and Data Review:		
(Draft)		L. Cassell
(Postaudit)		S. Godfrey
(Amendment no. 5)		G. Faist

Gerald Faist Jr. Date Released

STUDY IDENTIFICATION

3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery

Test Material:	Metoclopramide Nasal Spray; 10 mL bottles with spray applicators (200 mg/mL)
Sponsor:	Roberts Pharmaceutical Corporation 4 Industrial Way West Eatontown, New Jersey 07724-2274
Study Monitor:	David Haenick, PhD
Study Location:	Covance Laboratories Inc. 9200 Leesburg Pike Vienna, Virginia 22182-1699
Study Director:	Michael D. DuVall, DVM, PhD (703) 893-5400

Study Timetable
Study Initiation:
In-life Start Date:
In-life End Date:
Study Completion Date:

KEY PERSONNEL

3-Month Intranasal Study with Metoclopramide Nasal Spray in Cynomolgus Monkeys with a 1-Month Recovery

Study Director:	Michael D. DuVall, DVM, PhD
Study Toxicologist:	Sharon P. Dyke, BS
Study Coordinator:	Joy T. Palabrica, BA
Ophthalmology Examinations:	William E. Ridder, DVM, MS, PhD
Veterinarian:	William E. Ridder, DVM, MS, PhD
Clinical Pathologist:	Renée C. Pearson, MS, DVM, Diplomate, ACVP
Anatomic Pathologist:	Borge M. Ulland, DVM, Diplomate, ACVP
Biostatistician:	Ajit K. Thakur, PhD
Supervisor, Dose Formulations:	William Caparoon, AA
Supervisor, Laboratory Animal Medicine	Robert L. Ridgway, DVM, Diplomate, ACLAM
Supervisor, Large-Animal Toxicology:	Jeffery G. Linebaugh, LATg
Supervisor, Postlife and Clinical Pathology Laboratories:	Kelly Bell, BS

CONTENTS

Page

ABSTRACT 10

PURPOSE 11

REGULATORY COMPLIANCE 11

TEST AND CONTROL MATERIALS 11
Test Material 11
Control Material 11
Reserve (Archive) Samples 12
Disposition 12

TEST ANIMALS AND HUSBANDRY 12
Environmental Enrichment and Dietary Supplements 13
Randomization 13

PROCEDURES 14
Group Designations and Dosing Protocol 14
Dose Selection Rationale 14

DOSING PROCEDURES 15
Dose Preparation 15
Method of Administration 15
Reason for Dosing Route 15
Dose Analyses 15

ANTEMORTEM PROCEDURES 16
Observation of Animals 16
Bioavailability 16
Clinical Pathology 17

POSTMORTEM PROCEDURES 18
Necropsy 18
Organ Weights 18
Bone Marrow Smears 19
Tissue Preservation 19
Histopathology 20
Statistical Analyses 20
Record Retention 21

CONTENTS (continued)

Page

Results and Discussion 22
In-life Observations 22
Clinical Pathology 25
Anatomic Pathology 26
Toxicokinetic Analysis 26

CONCLUSIONS 27

PATHOLOGY REPORT 29

COMMENTS ON THE DATA 34

CODES, ABBREVIATIONS, AND UNITS 35
General Codes and Abbreviations 36
Codes for Clinical Pathology 38
Abbreviations for Clinical Hematology 42
Abbreviations for Clinical Chemistry 44
Abbreviations for Urine Chemistry 47
Abbreviations for Clinical Urinalysis 48
Codes for Anatomic Pathology 49

TABLES
1A - Summary of Clinical Observations 52
1B - Summary of Ophthalmic Findings 55
2 - Nasal Irritation Scoring 56
3 - Summary of Body Weight Data 83
4A - Summary of Clinical Hematology Data 85
4B - Summary of Clinical Chemistry Data 101
5 - Plasma Drug Level Data 121
6A - Incidence of Macroscopic Observations - Terminal Sacrifice 122
6B - Incidence of Macroscopic Observations - Recovery Sacrifice 129
7A - Summary of Organ Weight Data - Terminal Sacrifice 136
7B - Summary of Organ Weight Data - Recovery Sacrifice 148
8A - Incidence of Microscopic Observations - Terminal Sacrifice 160
8B - Incidence of Microscopic Observations - Recovery Sacrifice 166

CONTENTS (continued)

Page

FIGURES
Figure 1 175
Figure 2 176
Figure 3 177
Figure 4 178

APPENDIX 1
Protocol 180
Protocol Amendment No. 1 196
Protocol Amendment No. 2 197
Protocol Amendment No. 3 198
Protocol Amendment No. 4 200
Protocol Amendment No. 5 202
Protocol Deviations 204

APPENDIX 2
Individual Clinical Observations 206
Individual Animal Fate Data 271

APPENDIX 3
Individual Body Weight Data 273

APPENDIX 4
Individual Clinical Hematology Values 278
Individual Clinical Chemistry Values 304

APPENDIX 5
Individual Anatomic Pathology Data 325

CONTENTS (continued)

Page

APPENDIX 6
Toxicokinetic Report 370

APPENDIX 7
Final Analytical Report 391

ABSTRACT

The purpose of the study was to evaluate the toxicity and bioavailability of Metoclopramide Nasal Spray when administered by intranasal spray to cynomolgus monkeys for at least 13 weeks and to assess the reversibility of any effects after a 4-week recovery period.

Male and female cynomolgus monkeys were assigned to four groups (six/sex/group in Groups 1 and 4 and three/sex/group in Groups 2 and 3). Three monkeys/sex in Groups 1 and 4 were designated for recovery. Each group received dose preparations four times daily containing the control material or metoclopramide at a dose level of 40, 80, or 160 mg/animal/day.

Criteria evaluated during the study included survival, clinical observations, nasal irritation, body weights, ophthalmic examinations, clinical pathology, gross pathology, organ weights, and histopathology. Blood samples were analyzed to determine plasma levels of metoclopramide.

Four-times-daily administration of Metoclopramide Nasal Spray at dosages of 40, 80, and 160 mg/animal/day produced behavioral effects that were consistent with the known pharmacologic side-effects of metoclopramide: hypoactivity, somnolence, hyperactivity (increased stereotypical behaviors), and dissociative posturing. Their incidence and severity were dose-dependent and were most prevalent during Weeks 1-3. The 40 and 160 mg/animal/day females tended to have a greater incidence of hypoactivity than the males in these groups. In addition, all of the 160 mg/animal/day females exhibited intention tremors, whereas only four males in this group were affected. The erythrocyte mass was decreased in the males treated at the 160 mg/animal/day level. The latter findings suggested a gender difference in the effects of metoclopramide at the highest dosage evaluated.

In conclusion, pharmacologic effects were observed at all dose levels and a no-observable-effect level (NOEL) was not determined. Due to the severity and incidence of the hypoactivity and tremors among the females treated with 80 mg/animal/day and the males treated with 160 mg/animal/day, the no-observable-adverse-effect level (NOAEL) was determined to be 40 and 80 mg/animal/day in the females and males, respectively.

PURPOSE

This study was designed to evaluate the toxicity and bioavailability of Metoclopramide Nasal Spray when administered by intranasal spray four times daily to cynomolgus monkeys for at least 3 months and to assess the reversibility of any effects after a 4-week recovery period.

REGULATORY COMPLIANCE

The study, as performed by Covance, was conducted in compliance with the Food and Drug Administration Good Laboratory Practice Regulations as set forth in Title 21 of the United States Code of Federal Regulations, Part 58, issued December 22, 1978 (effective June 20, 1979), and with any applicable amendments.

The protocol was reviewed and approved by the Institutional Animal Care and Use Committee at Covance.

TEST AND CONTROL MATERIALS

Test Material

The test material, Metoclopramide Nasal Spray, Lot No. R980104, was received from Roberts Pharmaceutical Corporation, Ontario, Canada, on and stored at room temperature, protected from light. It was described as a clear, colorless liquid. Information on purity, stability, synthesis methods, composition, or other characteristics that define the test material is on file with the Sponsor.

Control Material

The control material, 0.9% sodium chloride injection, USP, Lot No. 46-165-DK, was received from Roberts Pharmaceutical Corporation, Ontario, Canada, on and was stored at room temperature. It was described as a clear, colorless liquid. Information on synthesis methods, composition, or other characteristics that define the